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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/697,147	10/29/2003	Jian Zhang	18136-1050 C1	1191

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EXAMINER	
BRANNOCK, MICHAEL T	
ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 11/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/697,147	ZHANG ET AL.	
	Examiner	Art Unit	
	Michael Brannock	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) *9,16-24 and 28-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-15 and 25-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *102903,011405*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application: Claims and Amendments

Applicant is notified that the amendment to the specification put forth on 10/29/2003 has been entered in full.

Claims 9, 16-24 and 28-42 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Applicant's response of 8/7/2006

Applicant's election with traverse of Group I, claims 1-8, 10-15, 25-27 is acknowledged. The traversal is on the grounds that a search of Groups I and II would not be a serious burden on the examiner; and that the combination of Groups I and II would be more consistent with accepted use and current classification. This is not found persuasive for the following reasons:

Under MPEP § 803, there are two criteria for a proper requirement for restriction between patentably distinct inventions:

(A) The inventions must be independent (see MPEP § 8702.01, 806.04, 808.01) **or** distinct as claimed (see MPEP § 806.05- §806.05(I)): and

(B) There must be a serious burden on the examiner if restriction is required (see MPEP § 803.02, § 806.04(a)- 806.04(I), § 808.01(a), and § 808.02).

Consistent with current patent practice, a serious search burden may be established by (A) separate classification thereof: (B) a separate status in the art when they are classifiable together: (C) a different field of search. These criteria were met in the above restriction. Further, a search is directed not only to art which would be anticipatory, but also to art that

would render the invention obvious. In the instant case, the antisense nucleic acids of Group II are structurally and functionally distinct from the nucleic acids of Group I - and have obtained a recognized distinction in the art as evidenced by their separate classification, as indicated in the previous office action. Thus, Groups I and II require divergent searches, and to search both inventions would be burdensome. Therefore, the restriction is maintained and made Final.

Specification

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reasons: The figures make reference to specific polynucleotide and/or polypeptide sequences; these references must contain a sequence identifier of the form: SEQ ID NO: X. The sequence identifier may be placed in the figure itself, or in the brief description of the figure. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4-8 and 25-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims require a nucleic acid molecule (e.g. an mRNA as in claim 1) and "sequences". It is unclear what the "sequences" recited in the claim refer to - it is unclear if these sequences are required to have any particular property, e.g. are the "sequences" recited in claim 1 required to encode a "VNO receptor protein"? In claims 6-8 it is unclear if the "sequences" need only hybridize to the expression vector or to the cDNA. It is suggested to Applicant that "polynucleotides" replace "sequences" and that commas be inserted into the claim to help define what part of the sentence these sequences are referring to, however, as it is unclear what Applicant's intentions are, it is not possible to effectively make suggestions as to this issue. Further, it is suggested that in claims 6-8 that the polynucleotides referred to as "sequences" be stipulated to unambiguously include or exclude sequences that merely bind to the expression vector.

The claims require that the nucleic acid hybridize under stringent conditions. The term "stringent conditions" is confusing because it is a relative term and encompasses conditions of varying degrees of stringency - such conditions determining the bounds of the claim. However, the art does not provide an unambiguous definition of the term "stringent conditions" and neither

is such a definition given for the term in the specification (page 17) which puts forth the metes and bounds of the claim Applicant is seeking protection for. It is suggested that the claims recite the actual conditions that applicant considers to be stringent, i.e., salt concentration and temperature conditions of incubations and washes.

Claim 3 contains an improper Markush group. It is improper to use the term "comprising" instead of "consisting of." Ex parte Dotter, 12 USPQ 382 (Bd. App. 1931).

Claim 8 requires "the encoded protein" yet it is unclear which protein this phrase is referring to, e.g. that encoded by the cDNA or other vector sequences. If Applicant deems it proper, one way to obviate this part of the rejection would be to replace this phrase with the phrase "the protein encoded by said cDNA".

Claims 25-27 require a nucleic acid that can be used to identify "related" pheromone receptors. The specification and/or the claims have not set forth what is and what is not considered to be "related". The specification merely indicates that "related" receptor sequences may share a level of homology of preferably about 30% (page 23). Thus, the specification does not assert that the related sequences have any minimum sequence identity with those disclosed. Further, the specification does not define the term "homology" in any meaningfully quantitative way. Thus, the metes and bounds of the claims can not be determined.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 10-15, 25-27 are rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. The claims are directed to polynucleotides encoding polypeptides of SEQ ID NO: 3, and truncated versions thereof e.g. SEQ ID NO: 4 and 6. The instant specification puts forth that the polypeptide is a human pheromone receptor (e.g. page 13), although the specification does not assert that the polypeptide binds any particular pheromone or any particular ligand. The state of the art, as reviewed by Zhang, J. et al., PNAS 100(8337-8341)2003, is doubtful of the existence of functional of pheromone receptors in humans.

The specification asserts that the polypeptide is useful in a screening method to determine what ligands may activate or inhibit the polypeptide and also to determine what the physiological effects of the polypeptide might be (see page 13 example). This proposed use lacks a specific and substantial utility. It is not a specific use because any integral membrane protein could be used in exactly the same way. Further, many polypeptides are known in the art, yet the polypeptides have no known function or known ligands. Any of these orphan clones could be used in the manner described in the specification for the claimed polypeptide.

Furthermore, the proposed use of the polypeptide to screen for ligands of the polypeptide or for biologic effects of the polypeptide is not a substantial utility. A substantial utility is a practical use which amounts to more than a starting point for further research and investigation

and does not require or constitute carrying out further research to identify or reasonably confirm what the practical use might ultimately be. For example, an assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would be a practical use of the material. However, a method of treating an unspecified disease or condition with a material that has no particular correlation with a disease would not constitute a substantial utility. Basic research, such as studying the properties of the claimed product or the mechanisms in which the product is involved, does not constitute a substantial utility.

The specification puts forth that the polypeptide could be involved in any number of disparate disease states, and could therefore be used as a diagnostic or therapeutic agent (see page 13, for example). A stated belief that a correlation exists between the polynucleotides or polypeptides and any number of diseases is not sufficient guidance to use the claimed polynucleotides to treat and/or diagnosis a particular disease; it merely defines a starting point for further research and investigation.

The instant application has failed to provide guidance as to how one of skill in the art could use the claimed invention in a way that constitutes a specific or substantial utility. The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed nucleic acids.

Claims 1-8, 10-15, 25-27 are also rejected under 35 U.S.C. § 112 first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art

would not know how to use the claimed invention so that it would operate as intended without undue experimentation.

Furthermore, the claims encompass polynucleotides which merely hybridize to the polynucleotides encoding SEQ ID NO: 3. Thus the claims encompass a vast genus of polynucleotides encoding polypeptide variants of the polypeptide of SEQ ID NO: 3, i.e. substitutions, deletions or insertions in a protein corresponding to SEQ ID NO: 3; should Applicant establish a specific and substantial utility for the claimed polynucleotides, Applicant has not provided sufficient guidance as to how to make and use the encoded polypeptides which are not 100% identical to the polypeptide of SEQ ID NO: 3, but which still retain a desired property of the polypeptide of SEQ ID NO: 3. The claims require polynucleotides comprising only portions which hybridize to a polynucleotide encoding SEQ ID NO: 3, e.g those that hybridize to a polynucleotide encoding a fragment of SEQ ID NO: 3. Thus, the vast majority of encoded polypeptides are amino acid sequence variants of SEQ ID NO: 3, i.e. amino acid substitutions, deletions or insertions in a protein corresponding to SEQ ID NO: 3, yet the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make. Furthermore, Applicant has not provided guidance as to what properties of the allelic variants or sequence variants of the protein corresponding to SEQ ID NO: 3 might be desired nor any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property. Applicant has not defined a difference in structure or difference in function between the protein corresponding to SEQ ID NO: 3 and variants of said protein. If a variant of the protein corresponding to SEQ ID NO: 3 is to have a structure and function similar to the protein corresponding to SEQ ID NO: 3, then the specification has failed to teach one of

skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the protein corresponding to SEQ ID NO: 3. Conversely, if a polynucleotide encoding a protein variant of SEQ ID NO: 3 need not have a disclosed property, the specification has failed to teach how to use such a polynucleotide.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2). Guo-HH et al. PNAS 101(25)9205-9210, 2004, recently reviewed the art and conducted an extensive study on the effect of amino acid substitution on the functionality of a wide variety of proteins and found that on average a single amino acid substitution had a 34% chance inactivating the functionality of the protein, see the Abstract.

However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Also, these or other regions may be critical determinants of antigenicity. It is well

appreciated in the art of antibody production that it is unpredictable which amino acids are critical antigenic determinants (see Alexander et al., Proc. Natl. Acad. Sci. 89(3352-3356)1992. Protein antigenicity can be significantly reduced by substitution of even a single residue. Further, even if an amino acid substitution does not destroy the activity of the immunizing protein, the substitution may significantly reduce the antigenicity of the protein (see the Abstract of Alexander et al.). The specification does not provide sufficient guidance as to how to make antibodies that are specific to variants of SEQ ID NO: 3 that can be used for any specific purpose. Although the specification suggests that polynucleotides that hybridize to the disclosed polynucleotides, under high, medium, or low stringency, can be used to find other "related" polynucleotides the specification has not indicated what exactly these other related polynucleotides can be used for - other than as a starting point for further research and investigation into the particular properties of the polynucleotides.

The specification has failed to provide an activity of SEQ ID NO: 3 to be used to evaluate the claimed variants for usefulness. The specification has not provided a working example of the use of the polypeptide of SEQ ID NO: 3 or a variant of the polypeptide of SEQ ID NO: 3 nor sufficient guidance so as to enable one of skill in the art to make such a variant with any particular use. The specification has failed to teach which amino acids of SEQ ID NO: 3 could be modified so as to produce a polypeptide that is not identical to SEQ ID NO: 3 and yet still retain the activity of the polypeptide of SEQ ID NO: 3 - which has apparently not been disclosed. The specification has not provided sufficient instruction as to how to find the activity of any such pheromone receptor polypeptide. The specification has provided no working example of a functional cloned pheromone receptor (from any species) and nor does such appear to be

recognized in the art. Commenting on the state of the art, Dulac et al.,Current Opinion in Neurobiology 10(511-118)2000, indicate that even in the field of rodent pheromone receptor biology, there exists a lack of functional studies able to match a pheromone ligand with a putative pheromone receptor, see page 512, col 2. The instant specification does not appear to address this art-recognized problem, yet the claims require methods of producing a pheromone receptor, i.e. a protein capable of recognizing a pheromone. The art does not appear to recognize the heterologous expression of a pheromone receptor in any host cell. Claims 6-15 require vectors and host cells capable of expressing a pheromone receptor. The specification provides no working example of such vectors and host cells, and merely asserts that such can be accomplished.

Thus, due to the large quantity of experimentation necessary to generate the infinite number of variants recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, the lack of direction provided in the specification as to how to use the encompassed variants, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 1, 2, 3-15 and 25-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses a polynucleotide of SEQ ID NO: 1 and two variants, yet the claims encompass a vast genus of polynucleotides not described in the specification, i.e. polynucleotides which comprise only portions of SEQ ID NO: 1, e.g. sequences from other species, mutated sequences, allelic variants, or sequences that can be used to identify related pheromone receptors. None of these sequences meet the written description provision of 35 U.S.C. 112, first paragraph. Although one of skill in the art would reasonably predict that these sequences exist, one would not be able make useful predictions as to the nucleotide positions or identities of those sequences based on the information disclosed in the specification.

The instant disclosure of a single polynucleotide, that of SEQ ID NO: 1 and two variants, encoding a polypeptide with no instantly disclosed specific activities, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, a single isolated polynucleotide sequence SEQ ID NO: 1 and two single nucleotide variants, which are not sufficient to describe the essentially limitless genera encompassed by the claims.

The instant claims are not directed to that which is disclosed as essential to the invention, i.e. something that is homologous to the parent SEQ ID NO: 1 and has the function of the parent polynucleotide. Thus, with the exception of the of the polynucleotides disclosed, and other polynucleotides which encode a polypeptide of SEQ ID NO: 3, the skilled artisan cannot envision encompassed variants. Therefore, only polynucleotides encoding a polypeptide of SEQ ID NO: 3, and polynucleotides *consisting* of fragments thereof, or polynucleotides consisting of fragments thereof and heterologous sequences (e.g. carrier or tag sequences), but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph.

Further, Claims 6-15 require vectors and host cells capable of expressing a pheromone receptor. The art does not appear to recognize the heterologous expression of a pheromone receptor in any host cell (see above). The specification provides no working example of such vectors and host cells, and merely asserts that such can be accomplished. Thus, the skilled artisan, with knowledge of the field of pheromone receptor biology, would not recognize that Applicant was in possession of such vectors and host cells.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 3 is rejected under 35 U.S.C. 102(b) as being anticipated by Saito et al., Molecular Brain Research 60(215-227)1998.

The claim requires a cDNA selected from the group comprising SEQ ID NO: 1, 2, 5, 7. The word "comprising" provides open language to the claim, and given the broadest reasonable interpretation, any cDNA may be in the claimed group. Saito et al. disclose cDNA molecules encoding vomeronasal receptors, see the Abstract and Materials and Methods section. It is suggested that substituting the word "comprising" with "consisting" would obviate this rejection.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867. Official papers filed by fax should be directed to **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

October 29, 2006

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER